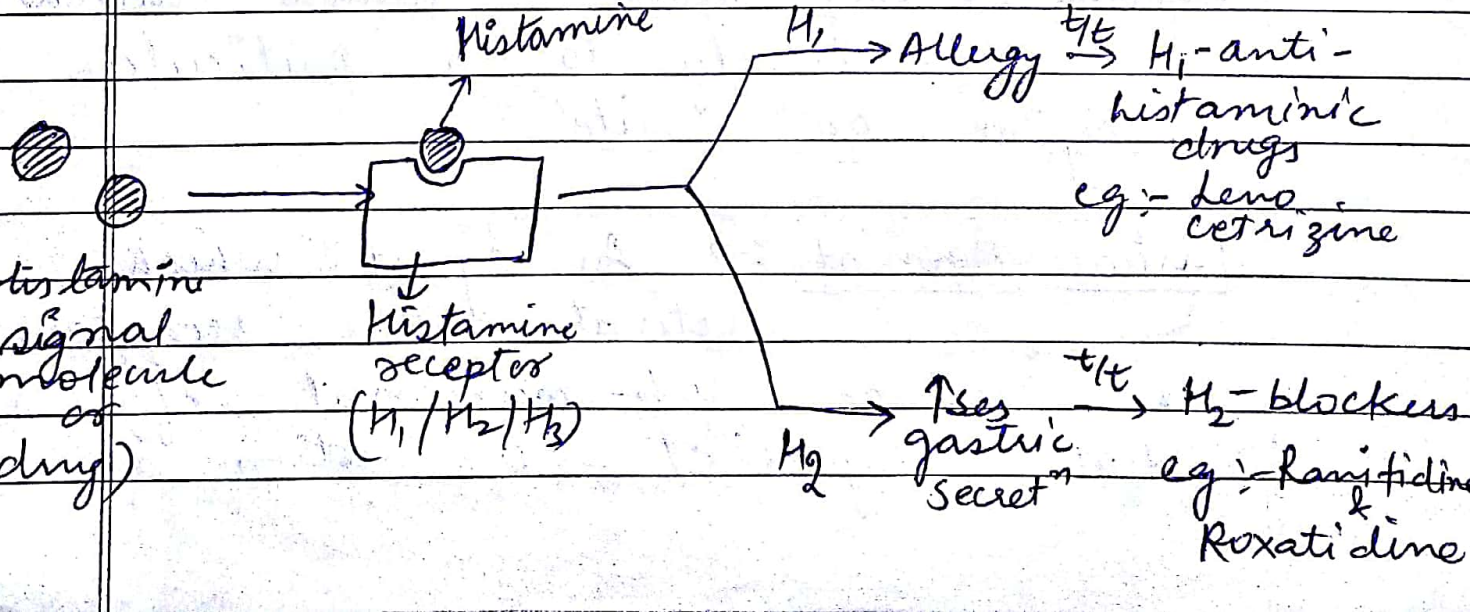
(1) **Receptors** ⇒ It is defined as macromolecule or binding site located on the surface or inside the effector cell that serves to recognise signal molecule or drug & initiates the response to it.

eg:⇒ Histamine gets binds to Histaminic receptors (H_1, H_2, H_3)



Receptor Subtypes:-

1. G-protein coupled receptors
2. Receptors with intrinsic ion channel
3. Enzyme linked receptors
4. Receptors regulating gene expression.

1. G-protein coupled receptors:- (GPCR)

These are a large family of cell membrane receptors which are linked to the effector (enzyme/channel / carrier protein) through one or more GTP-activated proteins (G-proteins) for response effectuation.

Structure:- The molecule has 7 α-helical membrane spanning hydrophobic amino acid (AA) segments which run into 3 extracellular and 3 intra-cellular loops. The agonist binding site is located somewhere b/w helices on extracellular face. while another recognition site formed by cytosolic segments binds the coupling G-proteins.

The G-proteins float in the membrane with their exposed domain lying in the cytosol and hetero-trimeric in composition (α, β & γ subunits). In inactive state GDP is bound to their exposed domain, activation through receptor leads to displacement of GDP by GTP.

The α-subunit carrying GTP dissociates from other two subunits (β & γ) and either activates or inhibits the effector.

The βγ subunits have shown to modulate certain effectors like receptor operated K^+ channels, adenylyl cyclase (AC) and phospholipase C.

Types of Gi-proteins :- depending upon the nature of α-subunits

G_{is} :-	Adenylyl cyclase ↑, Ca^{+2} channel ↑
G_{i1} :-	Adenylyl cyclase ↓, K^+ channel ↑
G_{i0} :-	Ca^{+2} channel ↓
G_{iq} :-	Phospholipase C ↑
G_{i3} :-	Na^+/H^+ exchange ↑

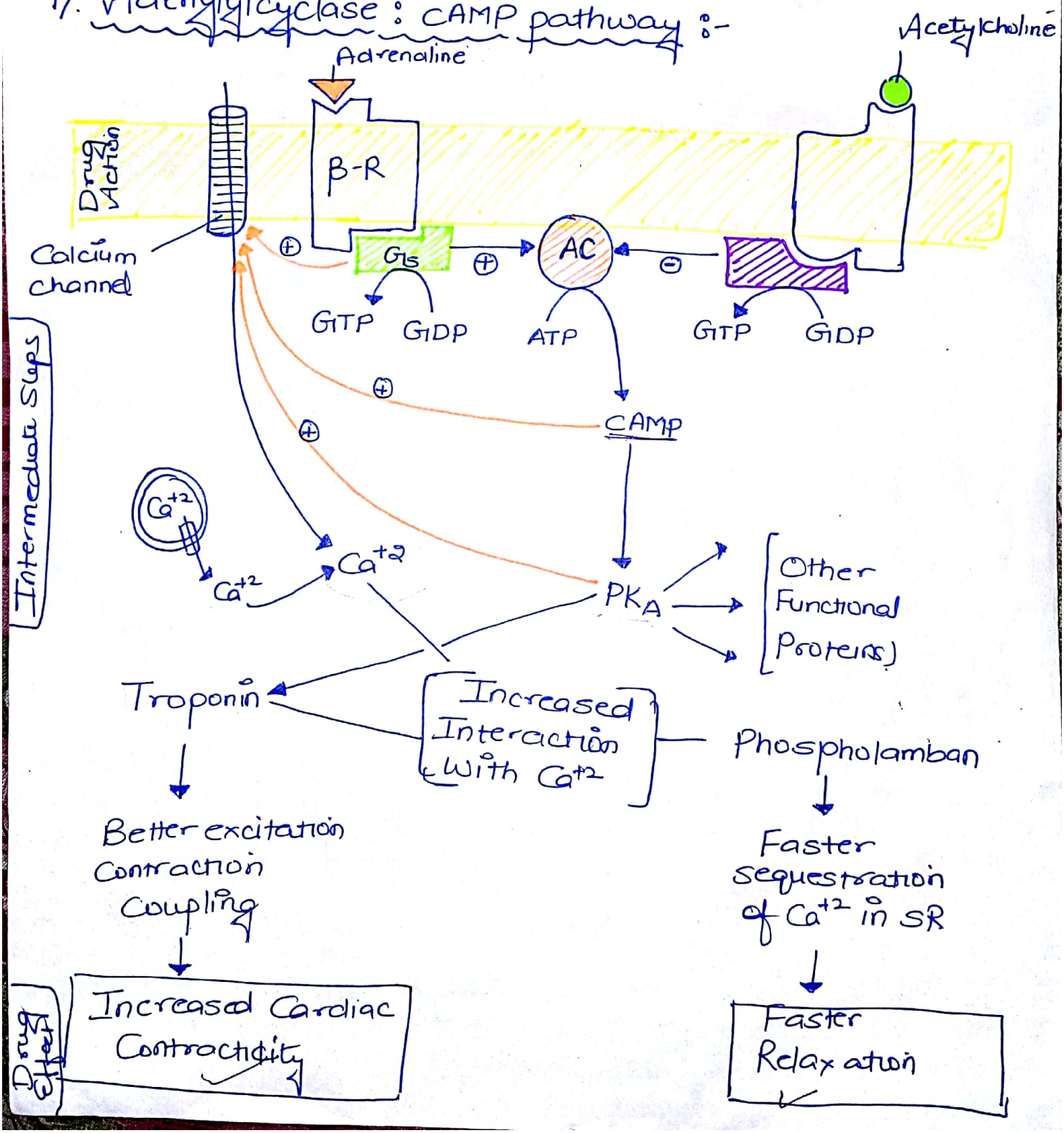
The α-subunit has GTPase activity. The bound GTP is slowly hydrolysed to GDP. The α-subunit then dissociates from the effector to regain its other subunits, but not before the effector has been activated/inhibited for a few seconds and the signal has been amplified

The onset time of response through this type of receptors is also in seconds.

Major Effector Pathways through which GPCRs function :-

1). Adenylylcyclase : cAMP pathway
2). Phospholipase C : IP_3 - DAG Pathway
3) Channel Regulation.

1). Adenylylcyclase : cAMP pathway :-



Activation of AC ⟶ results in intracellular accumulation of second messenger cAMP

↓

PKA (protein kinase A) is cAMP dependent which phosphorylates and alters the function of many enzymes, ion channels, transporters, and structural proteins to manifest as;

↓

- Increased contractility / impulse generation
- Relaxation (Smooth muscle)
- Glycogenolysis
- Lipolysis
- Inhibition of secretion
- mediator release
- modulation of junctional transmission.
- Hormone Synthesis etc.

Responses opposite to the above are produced when AC is inhibited through inhibitory G_i protein.

(a) Adrenaline :-

Adrenaline (Adr) → binds to β- adrenergic receptor (β-R) on the cell surface

↓

induce conformational change which permits interaction of Gi- protein binding site with stimulatory Gi- protein (Gis).

↓

Activated Gis then binds GTP (in place of GDP), causing its active subunit to dissociate

↓

then activates AC, located on the cytosolic side of the membrane.

↓

ATP is hydrolysed to cAMP

↓

cAMP phosphorylates and activates cAMP dependent protein kinase (PKA).

↓

PKA phosphorylates many functional proteins, troponin & phospholamban.

←

these proteins interact with Ca^{+2}

↑

Respectively resulting in increased force of contraction & faster relaxation

↑

Ca^{+2} is made available by entry from outside as well as from intracellular stores.

The other protein phosphorylated by cAMP is phosphorylase kinase. → activates enzyme phosphorylase

↓

resulting in breakdown of glycogen (glycogenolysis)

↓

which used as energy source for ↑sed contractility.

(b) Action of Acetylcholine (Ach) on M_2 receptor, also located in myocardial membrane, can similarly activate an inhibitory G-protein (G_i) which then opposes the activation of AC by G_s.

(2) Phospholipase C : IP_3-DAG Pathway :-

Phospholipase C → Hydrolyses → Membrane phospholipid Phosphatidyl inositol 4,5-biphosphate (PIP_2)

↑ Activation

↓ to generate

Second messenger Inositol 1,4,5-triphosphate (IP_3) and diacylglycerol (DAG)

$$PIP_2 \xrightarrow{\text{Phosphdipase C}} IP_3 + DAG$$

The IP_3 mobilises Ca^{+2} from intracellular organellar depots and DAG enhances protein kinase C (PKC) activation by Ca^{+2}.

Cytsolic Ca^{+2} (third messenger) is a versatile regulator

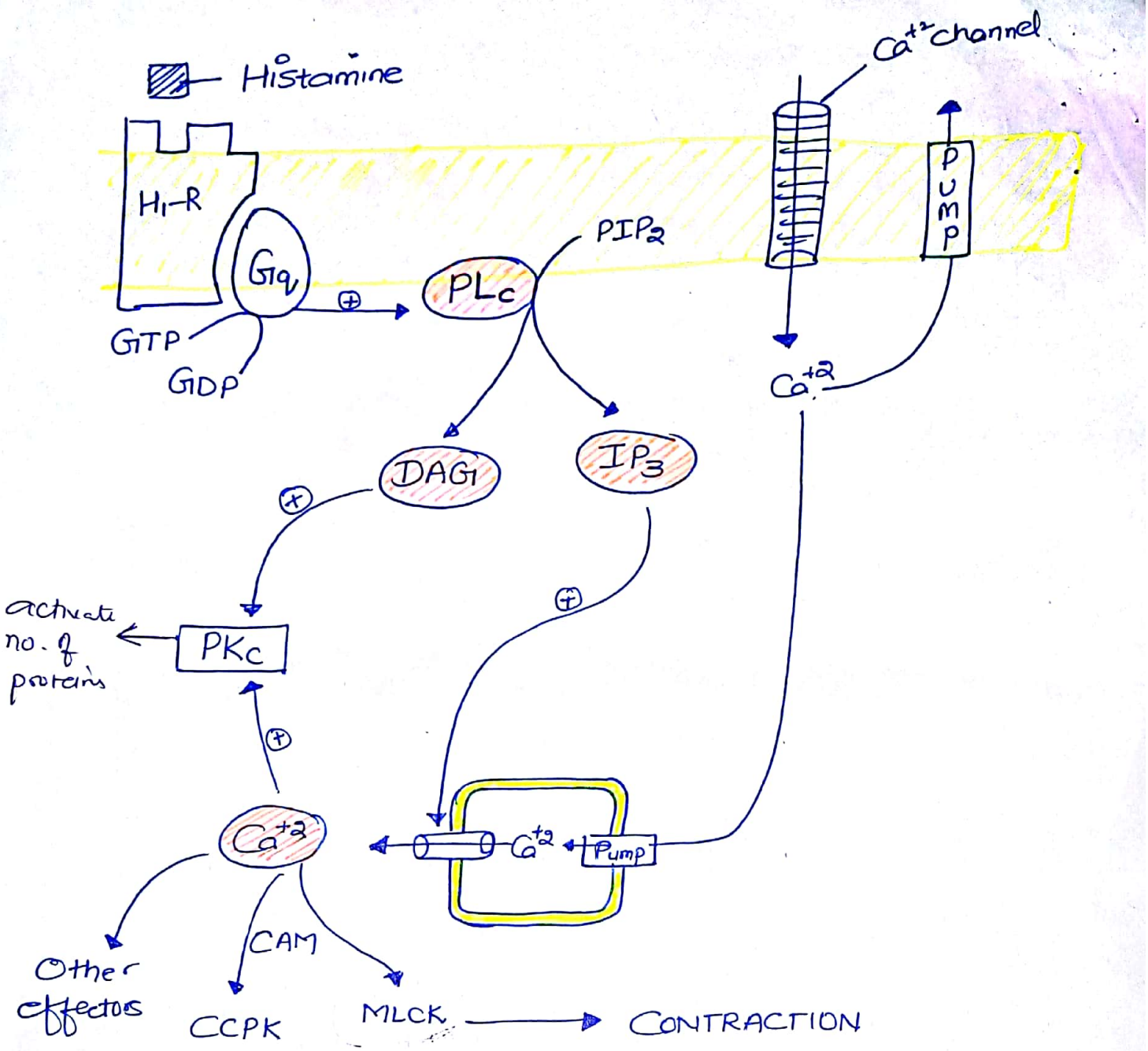
↓

acting through CAM (Calmodulin), PKC, and other effectors

↓

mediates ; – Contraction
- Secretion
- transmitter release
- eicosanoid synthesis,
- neuronal excitability
- Intracellular movements
- membrane function
- metabolism
- Cell proliferation.

eg: Binding of agonists such as thrombin to platelet surface receptors can trigger the activation of phospholipase C to catalyse the release of archiodonic acid. Arachiodonic acid can then go on into COX & LOX pathway.



Histamine → binds to H_1 receptor (H_1-R)

↓

activates Gq (protein)

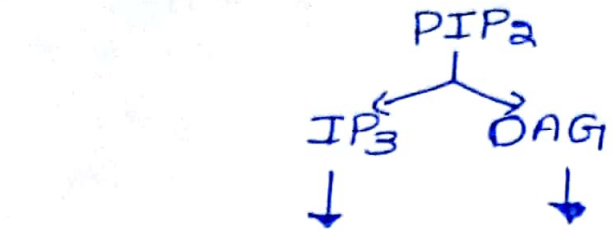
↓

which activates PLc (1st)

↓

PLc hydrolyse PIP → DAG and IP_3 (2nd)

→ P.T.O



Facilitate Ca^{+2} mobilization from intracellular pools

In conjunction with Ca^{+2}, activates protein kinase C (PKC)

PKC phosphorylates and alters the activity of a number of functional and structural proteins

Ca^{+2} is a veritable messenger : combines with CAM (Calmodulin – Ca^{+2} binding protein) to activate MLCK (Myosin light chain kinase) which induce contraction.

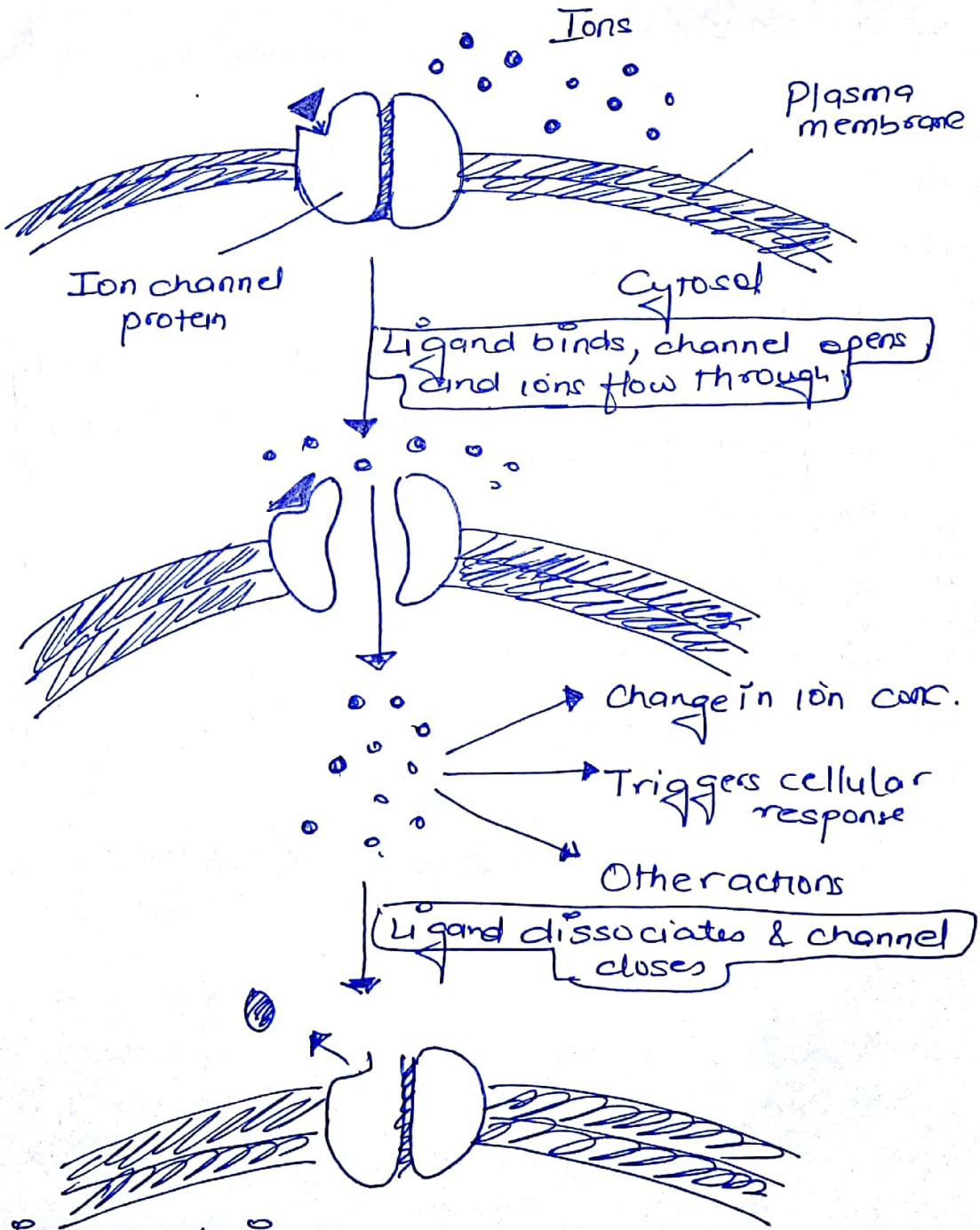
And also form Calcium-Calmodulin protein kinase. Several other effectors are regulated by Ca^{+2} in a CAM dependent or independent manner.

(c) Channel regulation :- The activated G-proteins can also open or close ionic channels specific for Ca^{+2}, K^+ or Na^+ without the intervention of any second messenger like cAMP or IP_3 and bring about hyperpolarization depolarization / change in intracellular Ca^{+2}.

The G_s opens Ca^{+2} channels in myocardium and skeletal muscles while G_i and G_o open K^+ channel in heart and smooth muscle as well as close neuronal Ca^{+2} channels.

(2) Receptors with intrinsic ion channel :-
(Ligand - gated ion channel) LIC

These are ionotropic receptors, or are a group of transmembrane ion channel proteins which open to allow ions such as Na^+, K^+, Ca^{+2} and ord- to pass through the membrane in response to the binding of chemical messenger (Ligand) such as neurotransmitter.



These are important in nervous system.

For examples:- GABAA- glycine, 5-HT3 receptors.

Thus, in these receptors, agonist directly operation channels without the intervention of any coupling protein or second messenger.

The onset and offset of responses through this class of receptor is the fastest (in miliseces.)

(3) Enzyme linked receptors:-

It is transmembrane receptor, where the binding of an extracellular ligand causes enzymatic activity on the intracellular side.

These receptors have a subunit with enzymatic property or bind a JAK (Janus Kinase) enzyme on activation.

The agonist binding site and the catalytic site lie respectively on the outer and inner face of the plasma membrane.

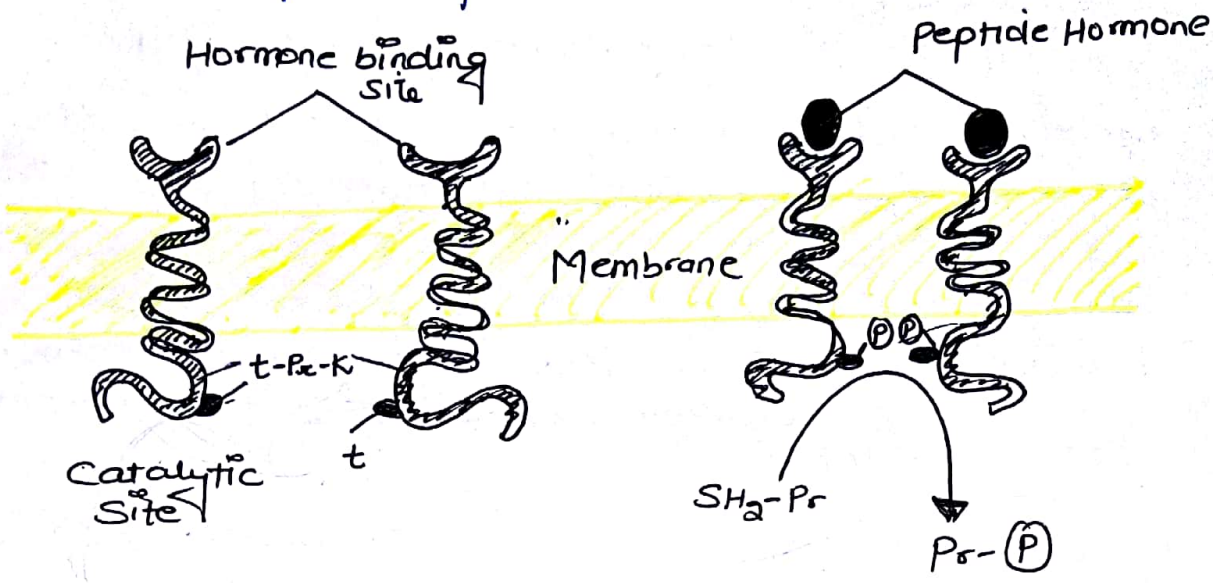
These two domains are interconnected through a single transmembrane stretch of peptide chain.

Types of Enzyme linked receptors

(a) Those that have intrinsic enzymatic activity

(b) Those that lack intrinsic enzymatic activity, but bind a JAK-STAT Kinase on activation.

(A) Intrinsic tyrosine protein kinase receptor:-



Peptide hormone binds to extracellular domain → monomeric receptors move laterally in membrane & form dimers

↓

Dimerization activates tyrosine-protein kinase activity of intracellular domain.

↓

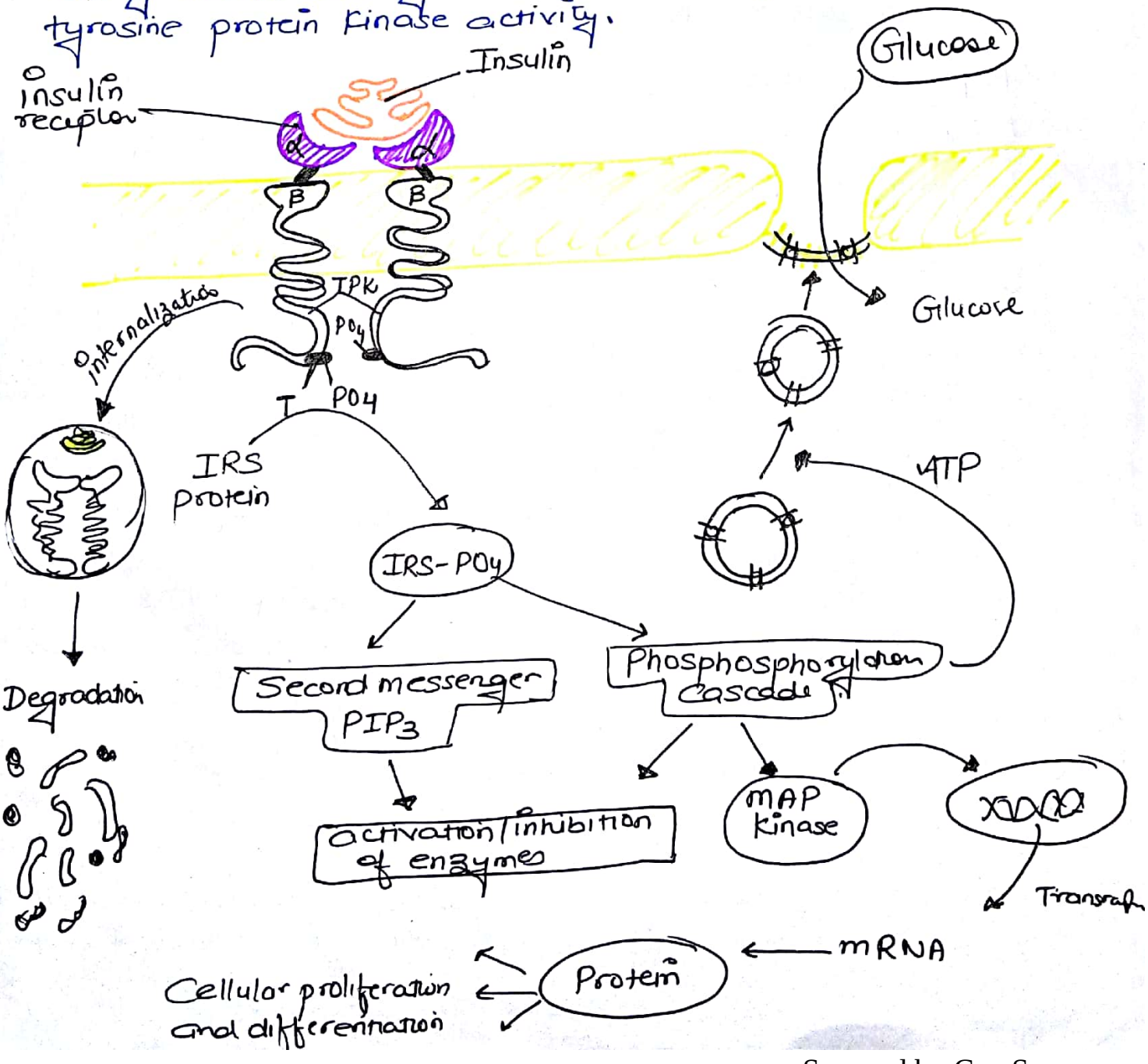
these domain phosphorylate tyrosine (t) residues on each other as on several SH_2 domain Substrate protein (SH_2-Pr)

↓

The phosphorylated substrate protein then perform downstream signalling function.
eg. Insulin Receptor.

Insulin Receptor:- Insulin acts on specific receptors located on the cell membrane of practically every cell but their density depends on the cell type : Liver & fat cells are very rich.

Structure :- Insulin receptor is a heterotetrameric glycoprotein consisting of 2 extracellular α and 2 transmembrane β- subunits linked together by disulfide bonds. It is oriented across the cell membrane as a heterodimer. The α- subunits carry insulin binding site, while the β- subunit have tyrosine protein kinase activity.



Insulin binds to α-subunits of receptor → induces aggregation and internalization of receptor along with bound insulin molecules.

↓

this activates tyrosine kinase activity of β-Subunits.

↓

pairs of β-subunit phosphorylate tyrosine residues on each other

↓

expose the catalytic site to phosphorylate tyrosine residues of insulin Receptor substrate proteins.

↓

In turn, cascade of phosphorylation and de-phosphorylation reaction is set into motion

↓

Resulting in stimulation or inhibition of enzymes involved in rapid metabolic action of insulin.

IRS :- Insulin Receptor Substrate Protein

MAP Kinase:- Mitogen-activated protein kinase (MAPK)

→ Certain second messengers like PIP_3 (phosphotidyl inositol triphosphate) which are generated through activation of specific PI3-Kinase.

→ Insulin stimulates glucose transport across cell membrane by ATP dependent translocation of glucose transporter GLUT4 and GLUT1 to the plasma membrane as well as by increasing its activity.

→ Insulin also regulate no. of genes for a large no. of enzymes such as MAP Kinases.

·Activation of transcription factors also promotes proliferation and differentiation of specific cells.

→ The internalized receptor–insulin complex is either degraded intracellularly or returned back to the surface from where the insulin is released extracellularly.

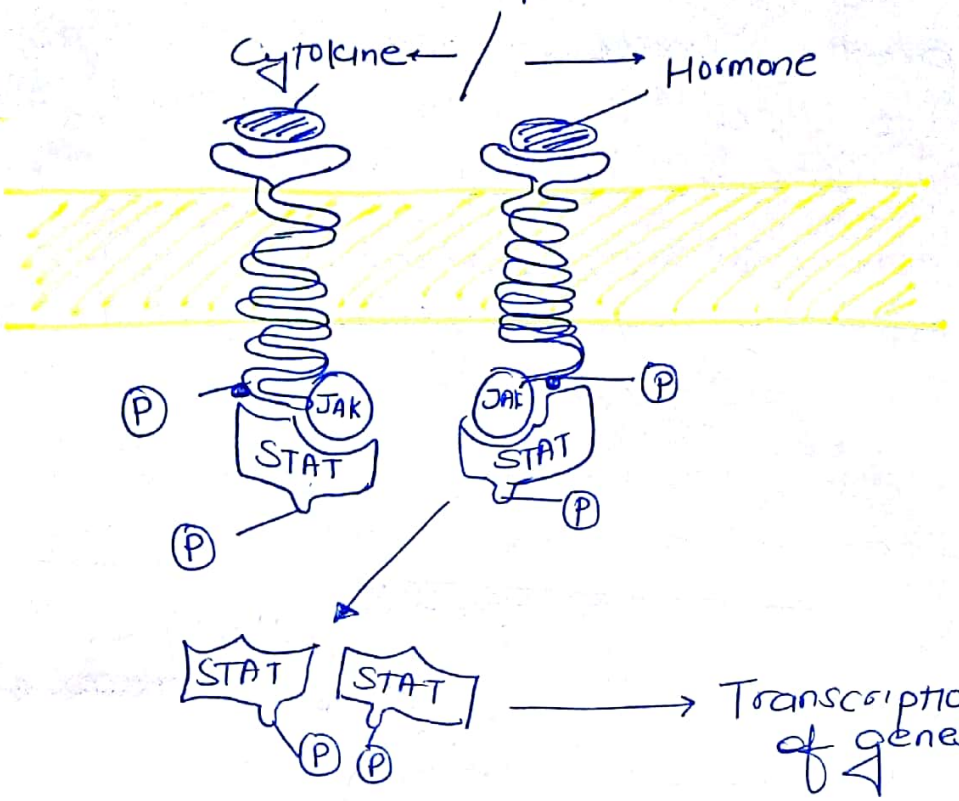
(B) JAK-STAT Kinase binding receptors :-

These receptors differ in not having any intrinsic catalytic domain. Agonist induced dimerization alters the intracellular domain Conformation to increase its affinity for a Cytosolic tyrosine protein kinase JAK.

On binding, JAK gets activated and phosphorylates tyrosine residues of the receptor which now binds another free moving protein STAT (Signal transducer & activator of transcription). which is also phosphorylated by JAK.

Pairs of Phosphorylated STAT dimerize and translocate to nucleus to regulate gene transcription → to give response.

(B) JAK-STAT KINASE binding Receptor :-



Signal molecule binds to the receptor → which induces receptor dimerization

↓

which activates intracellular domain to bind free moving JAK (Janus Kinase) molecules.

↓

The activated JAK phosphorylate tyrosine residues on the receptor

↓

which then binds another protein STAT.

↓

Tyrosine residues of STAT also get phosphorylated by JAK.

← The phosphorylated STAT dimerize, dissociate from the receptor

↑

then move to the nucleus

↑

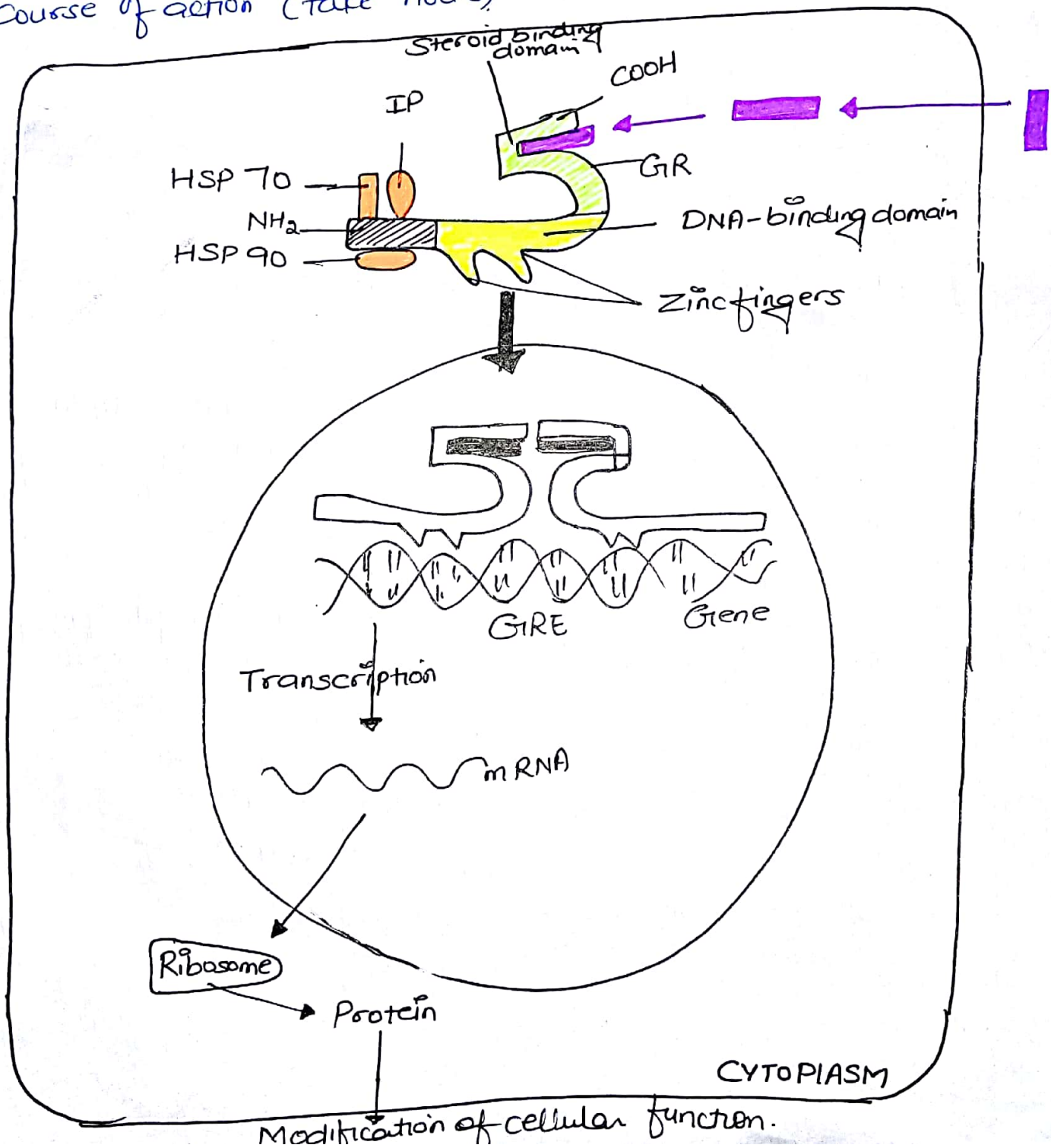
to regulate transcription of target genes.

④ Receptors regulating gene expression :-

These are the intracellular soluble protein which respond to lipid soluble chemical messengers that penerate the cell.

All steroidal hormones (glucocorticoids, mineralocorticoids, androgens, estrogens), Vit D, Vit A, thyroid hormones function in this manner.

The transduction mechanism is slowest in its time course of action (take hours)



Glucocorticoid penetrates the cell membrane → Binds to glucocorticoid receptor protein (GR) that carry three proteins; Heat shock protein 70, 90 and IP(immunophilin. → GR has a steroid binding domain near COOH terminus & amid region DNA binding domain having zinc fingers.

↓

Zinc fingers made up of loop of amino acids with chelated zinc ion.

↓

Binding of steroid to GR dissociates the complexed proteins (HSP90) etc. removing their inhibitory influence on it.

↓

A dimerization region that overlaps the steroid binding domain is exposed

↓

promoting dimerization of occupied receptor

↓

Steroid bound receptor diamer translocates to the nucleus → Interacts with specific DNA sequences called glucocorticoid responsive elements (GREs) within regulatory region of appropriate genes.

↑

Expression of these genes is consequently altered resulting in promotion of their transcription

↑

MRNA thus produced is directed to the ribosome

↑

where message is translated into specific pattern of protein synthesis

↑

which inturn modifies cell function.

ADME

Absorption :- It is the movement of the drug from its site of administration into the circulation.

Factors affecting the absorption are :-

1) **Aqueous solubility :-**

Drugs given in solid form (tablet / capsules) must dissolve in the aqueous biophase before they are absorbed.

For poorly water soluble drugs eg: Aspirin, Griseofulvin, the rate of dissolution govers the rate of absorption.

A drug given as watery solution is absorbed faster than when the same is given in solid form.

2) **Concentration :-**

Passive diffusion depends on concentration gradient.

Drug given as concentrated solution is absorbed faster than from dilute solution.

3) **Area of absorbing surface :-** Larger the absorbing surface, faster is the absorption.

④ Vascularity of the absorbing surface:-

Blood circulation removes the drug from the site of injection absorption and maintains the concentration gradient across the absorbing surface.

Increased blood flow hastens drug absorption just as wind hastens drying of clothes.

⑤ Route of administration:-

This affects drug absorption, because each route has its own peculiarities.

Bioavailability :-

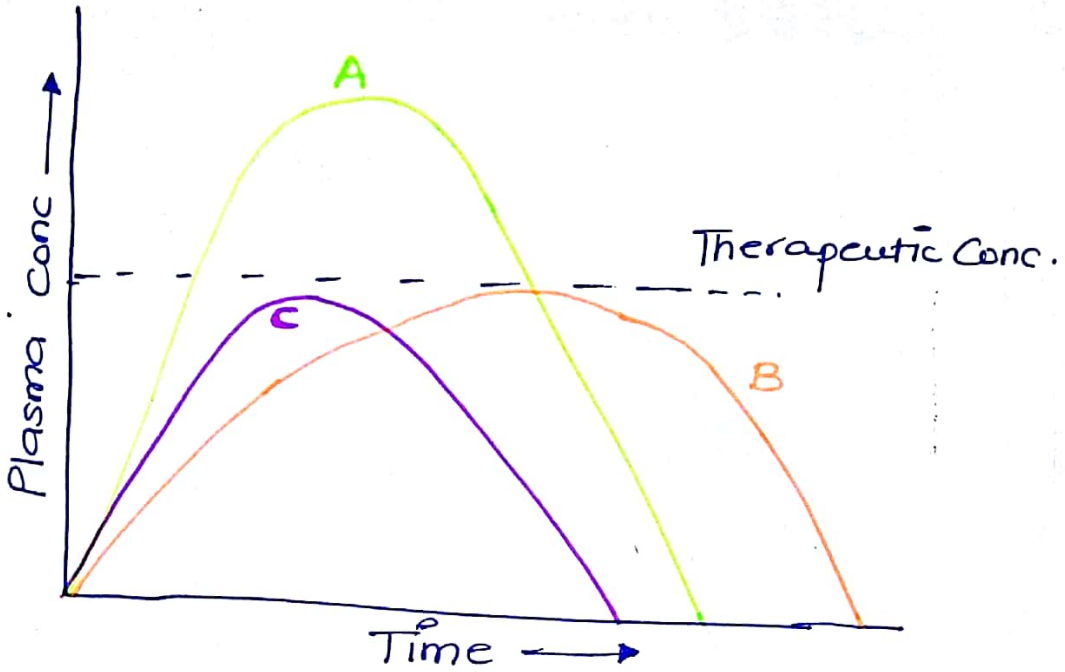
It refers to the rate and extent of absorption of drug from a dosage form as determined by its concentration time curve in blood or by its excretion in urine.

It is a measure of fraction of administered dose of a drug that reaches the systemic circulation in the unchanged form.

Bioavailability of drug injected I.V is 100%. but is frequently lower after oral ingestion because :-

(a) the drug may be incompletely absorbed.

(b) the absorbed drug may undergo first pass metabolism in the intestinal wall / liver or excreted in bile.



Plasma conc-time curve depicting bioavailability differences b/w three prepn of a drug containing the same amount.

Formulation B:- is more slowly absorbed than A and though ultimately both are absorbed to the same extent, B may not produce therapeutic effect.

Formulation C:- is absorbed to a lesser extent - lower bioavailability.

Oral formulations of a drug from different manufacturers or different batches from same manufacturer may have the same amount of drug but may not yield the same blood levels - are called biologically inequivalent.

Bioequivalent Preparations:- Two preparations of a drug are considered bioequivalent when the rate and extent of bioavailability of the drug from them is not significantly different under suitable test conditions.

Distribution:- In this, drug get distributed to other tissues that initially had no drug after they absorbed in the circulation.

Factors affecting distribution are:-

- Lipid solubility
- Ionization at physiological pH
- Extent of binding to plasma and tissue proteins
- Presence of tissue specific transporters.
- Regional blood flow.

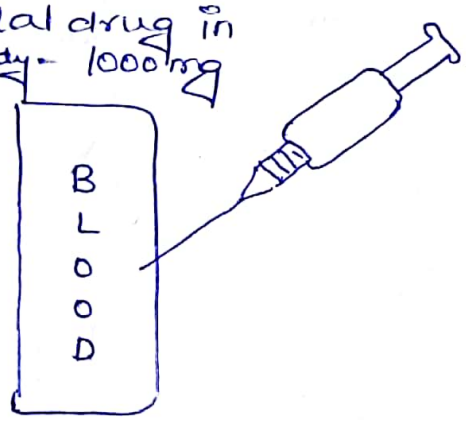
Movement of drug proceeds until an equilibrium is established b/w unbound drug in plasma & tissue fluids.

Subsequently, there is a parallel decline in both due to elimination.

Apparent volume of distribution (V):- The volume that would accommodate all the drug in the body, if the concentration throughout was the same as in plasma.

$$V = \frac{\text{dose administered I.V}}{\text{plasma concentration}}$$

eg:- Total drug in the body - 1000mg



Plasma drug concentration = 50mg/L

$$V = \frac{1000}{50} = 20L$$

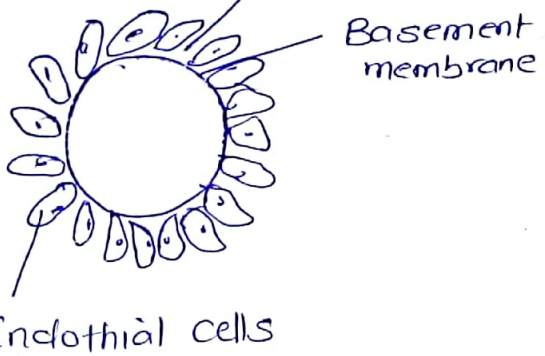
Redistribution:- Highly lipid soluble drugs get initially distributed to organs with high blood flow ie. brain, heart, kidney etc. Later less vascular but more bulky tissues (muscles, fat) take up the drug - plasma concentration falls and the drug is withdrawn from these sites.

Greater the lipid solubility of the drug, faster is its redistribution.

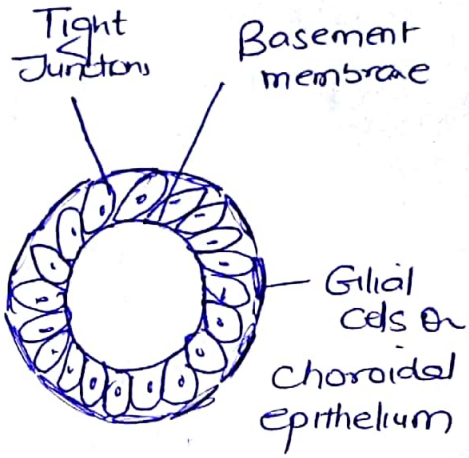
eg:-

Penetration into brain and CSF:-

The capillary endothelial cells in brain have tight junctions and lack large paracellular spaces. Further, neural tissue covers the capillaries. Together they constitute the so called blood brain barrier (BBB).



Usual capillary



Brain capillary

Blood-CSF barrier is located in the choroid plexus. Capillaries are lined by choroidal epithelium having tight junctions.

Both these barries are lipoidal and limit the entry of nonlipid soluble drugs eg: Streptomycin Neostigmine etc.

Only lipid soluble drugs, therefore are able to penetrate and have achon on the central nervous System.

Passage across placenta :-

Placental membrane are lipoidal and allow free passage of lipophilic drugs while restricting hydrophilic drugs.

Also like brain, efflux transporters like P-gp and BCRP, MRP3 also serve to limit foetal exposure to maternally administered drugs.

Placenta is a site for drug metabolism as well, which may lower/modify exposure of the foetus to administered drug.

However, restricted amounts of nonlipid-soluble drugs, when present in high concentration or for long periods in maternal circulation, gain access to the foetus.

Placenta also contain certain influx transporters. Thus, it is an incomplete barrier and almost any drug taken by the mother can affect the foetus or the newborn.

Plasma protein binding :-

Most drugs possess physiochemical affinity for plasma proteins and get reversibly bound to these.

Acidic drugs ⟶ bound to plasma albumin

Basic drugs ⟶ bound to α_1 acid glycoprotein.

Significant implications of plasma protein binding :-

1). Highly plasma protein bound drugs are largely restricted to the vascular compartment because protein bound drug does not cross membrane. They tend to have smaller volume of distribution.

2). The bound fraction is not available for action. However, it is in equilibrium with the free drug in plasma and dissociates when conc. of the latter is reduced due to elimination.

3). High degree of protein binding generally makes the drug long acting, because bound fraction is not available for metabolism or excretion, unless, it is actively extracted by liver or kidney.

4). The generally expressed plasma concentration of drug refer to bound as well as free drug. Degree of protein binding should be taken into account while relating these to concentrations of drug that are active in vitro.

eg : MIC of an antimicrobial.

5). One drug can bind to many sites on the albumin molecule. Conversely, more than one drug can bind to the same site.

This can give rise to displacement interactions among drugs bound to same site.

The drug bound with high affinity will displace that bound with lower affinity.

eg:- Aspirin displaces sulfonylureas

Indomethacin, phenytoin displace warfarin.

potentiates anticoagulant effect.

(6) In hypoalbuminemia, binding may be reduced and high concentrations of free drug may be attained eg: Phenytoin & Furosemide.

Other disease condition can also affect protein binding :- eg:-

Propranolol binding is increased in pregnant women.

(II) Biotransformation :-
(Metabolism)

It means chemical alteration of the drug in the body.

It is needed to render (non polar) lipid soluble compound polar (lipid insoluble) so that they are not reabsorbed in renal tubules and are excreted.

Lipid soluble (non-polar) drug $\xrightarrow{\text{Chemical alteration}}$ Non-lipid soluble (polar) drug

↓

Not reabsorbed in renal tubules

↓

Finally excreted.

eg:- Most hydrophilic drugs eg:- Streptomycin, neostigmine, pancuronium etc are little biotransformed and are largely excreted unchanged.

Site for drug metabolism:- Primary site is Liver. Other include, Kidney intestine, lungs and plasma.

Biotransformation of drugs may lead to the following:-

(a) Inactivation:- Most drugs and their active metabolites are rendered inactive or less active eg: Ibuprofen, paracetamol, Lidocaine, chloramphenicol etc.

(b) Active metabolite from an active drug:- Many drugs have been found to be partially converted to one or more active metabolites.

The effects observed are the sum total of that due to the parent drug and its active metabolite.

Eg:- active drug	Digitoxin	→ Digoxin	active metabolite
	Codeine	→ Morphine	
	Amitriptyline	→ Nortriptyline	
	Allopurinol	→ Alloxanthine	

③ Activation of inactive drug :- Last Page: 8.

Types of Biotransformation Rxns

Phase I or Non-synthetic or Functionalization Reactions

↓

Functional group is generated or exposed

↓

metabolite may be active or inactive.

Phase II or Synthetic or Conjugation Reactions

↓

Eng Endogenous radical is conjugated to the drug metabolite

↓

Mostly metabolite is inactive.

except :-
glucuronide conjugate of morphine and Sulfate conjugate of minoxidil are active.

Non-Synthetic Rxns :-

(1) **Oxidation :-** This reaction involves addition of O_2 and removal of hydrogen.

These rxns are mostly carried out by group of monooxygenases in liver, which in final step involve a cytochrome P450 hemoprotein, NADPH, Cytochrome P450 reductase and molecular O_2.

(2) **Reduction :-** This rxn is converse of oxidation and involves cytochrome P450 enzymes working in the opposite direction

(3) **Hydrolysis :-** This is cleavage of drug molecule by taking up a molecule of water.

$$\text{Ester} + H_2O \xrightarrow{\text{esterase}} \text{Acid} + \text{Alcohol}$$

(4) **Cyclization :-** This is formation of ring structure from a straight chain compound.
eg:- Proguanil.

(5) **Decyclization :-** This is opening up of ring structure of the cyclic drug molecule eg: Barbiturates, phenytoin. This is generally a minor pathway.

Synthetic Rxns :-

(1) **Glucuronide conjugation :-**

Glucose $\xrightarrow{\text{form}}$ Glucuronic acid $\longrightarrow$ which conjugate with compounds having a hydroxyl or carboxylic acid group.

eg:- Chloramphenical, aspirin, paracetamol, diazepam, morphine.

Glucuronidation increases the molecular weight of the drug which favours its excretion in bile.

(2) Acetylation :-

Compounds having amino or hydrazine residues are conjugated with the help of acetyl coenzyme A

eg:- Sulfonamides.

(3) Methylation :-

The amines and phenols can be methylated by methyl transferase.

eg:- Adrenaline, Captopril, histamine etc.

(4) Sulfate conjugation :-

The phenolic compounds and steroids are sulfated by sulfotransferases eg:- Methyldopa.

(5) Glycine conjugation :-

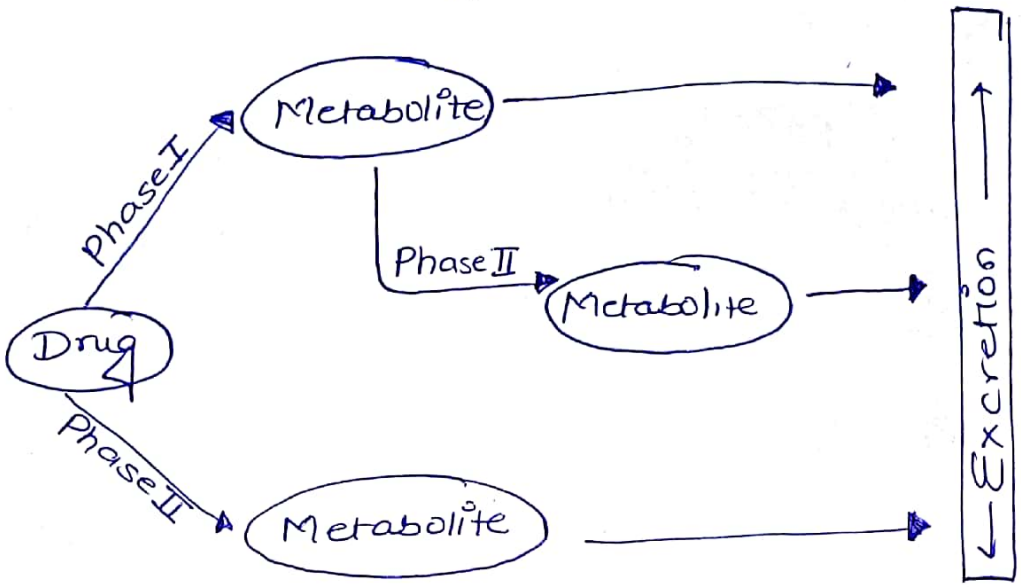
Salicylates, nicotinic acid & other drugs having carboxylic acid group are conjugated with glycine.

(6) Glutathione conjugation :-

This is carried out by glutathione-S-transferase forming a mercapturate. It is normally a minor pathway.

⑦ Ribonucleoside / nucleotide synthesis :-

This pathway is important for the activation of many purine and pyrimidine antimetabolites used in cancer chemotherapy.



(V) Excretion :-

It is the passage out of systemically absorbed drug.

Drugs and their metabolites are excreted in :-

① Urine :- Through the kidney. It is most important channel of excretion for the majority of drugs.

② Faeces :- Apart from the unabsorbed fraction, most of the drug present in faeces is derived from bile.

Certain drugs are excreted directly in Colon eg :- Anthracene purgatives, heavy metals.

③ Exhaled air :-

Gases and volatile liquids are eliminated by lungs, irrespective of their lipid solubility.

④ Saliva and Sweat :-

These are of minor importance for drug excretion. Lithium, Rifampin and heavy metals are present in these secretions in significant amounts.

⑤ Milk :- The excretion of drug in milk is not important for the mother, but the suckling infants inadvertently receives the drug.

First Pass (Presystemic) metabolism :-

This refers to metabolism of a drug during its passage from site of absorption into systemic circulation.

All orally administered drugs are exposed to drug metabolizing enzymes in intestinal wall and liver (where they first reach through portal vein.

→ Oral dose is considerably higher than sublingual or parenteral dose.

→ Oral bioavailability is apparently increased in patients with severe liver disease.

→ Oral bioavailability of a drug is increased if another drug competing with it in first pass metabolism is given concurrently eg :-

Eg- Chlorpromazine and Propanolol.

(III) Activation of inactive drug :-

Few drugs are inactive as such and need conversion in the body to one or more active metabolites. Such a drug is called Prodrug.

eg:-

Prodrug		Active form		
Levodopa	⟶	dopamine	⟶	Parkinsonism disease
Enalpril	⟶	Enalaprilat	⟶	Hypertension
Acyclovir	⟶	Acyclovir tri-phosphate	⟶	Viral infections.

Adverse Drug Effects

Adverse effect is any undesirable or unintended consequence of drug administration.

Adverse drug reaction (ADR) has been defined as any noxious change which is suspected to be due to a drug, occurs at the doses normally used in man, requires treatment or decrease in dose or indicates caution in the future use of the same drug.

These effects may develop promptly or only after prolonged medication or even after stoppage of the drug.

Types of Adverse Effects

Predictable (Type A or Augmented) rxns

↓

Based on pharmacological properties of the drug include side effects, toxic effects & consequences of drug withdrawal.

↓

more common, dose related, & mostly preventable & reversible.

Unpredictable (Type B or Bizarre) rxns

↓

Based on peculiarities of the patient and not on drug's known actions. include; Idiosyncrasy, allergy.

↓

Some rxns can be predicted & prevented if genetic basis is known.

① Side effects :-

These are the unwanted but often unavoidable pharmacodynamic effects that occur at therapeutic doses.

Generally they are not serious, can be predicted from pharmacological profile of a drug.

Reduction in dose, usually reduces the symptoms.

eg :-

Glyceryl trinitrate (GTN) ⟶ Used in angina pectoris to relieve pain by dilating vasculature.

⟶ (⊗) this dilation also lead to hypotension & throbbing headache.

② Secondary effects :-

These are indirect consequences of a primary action of the drug eg :- Suppression of bacterial flora by tetracyclines paves the way for super-infection; corticosteroids weaken host defence mechanism so that latent tuberculosis gets activated.

③ Toxic effects :-

These are the result of excessive pharmacological action of the drug due to overdosage or prolonged use.

Overdosage may be absolute (accidental, homicidal, suicidal) or relative (ie usual dose of gentamicin in presence of renal failure).

eg :- (i) Morphine (analgesic) causes respiratory failure in overdosage.

(ii) Imipramine (anti-depressant) overdosage cause cardiac arrhythmias.

(iii) Streptomycin (anti-tubercular) causes vestibule damage on prolonged use.

④ Intolerance :- It is the appearance of characteristic toxic effects of a drug in an individual at therapeutic doses.

It is the converse of tolerance and indicates a low threshold of the individual to action of a drug.

eg :- A single dose of trifluopromazine induces muscular dystonias in some individuals, specially children.

⑤ Idiosyncrasy :-

It is genetically determined abnormal reactivity to a chemical.

The drug interacts with some unique feature of the individual, not found in majority of subjects, and produces the uncharacteristic reaction.

Eg :- Barbiturates causes excitement and mental confusion in some individuals.

Quinine / Quinidine cause cramps, diorrhoea, asthma and vascular collapse in some patients.

⑥ Drug allergy :-

It is an immunologically mediated reaction producing stereotype symptoms which are unrelated to the pharmacodynamic profile of the drug / generally occur even with much smaller dose and have a different time course of onset and duration. This is also called drug hyper-sensitivity.

The target organs primarily affected in drug allergy are skin, airways, blood vessels, blood & gastro-intestinal tract.

Mechanism and types of allergic reactions

(A) Humoral

(B) Cell mediated

(A) Humoral :-

(i) Type-I (anaphylactic reactions) :-

Reaginic antibodies IgE are produced

↓

get fixed to mast cells

↓

On exposure to a drug AG:AB reaction takes place on the mast cell surface.

↓

Release mediators like histamine, SHT, leukotrienes (LT-C4 & D4), Prostaglandins etc

↓

Resulting in urticaria, itching, angioedema, bronchospasm, rhinitis .etc.

↓

Manifestations occur quickly after challenge and are called Immediate hypersensitivity

↓

Anti-histaminics drugs are beneficial in these rxns

Type II (Cytolytic) Rxns :-

Drug + Component of specific tissue cell acts as AG.

↓

The resulting antibodies (IgG, IgM) bind to the target cells.

↓

On Reexposure AG: AB rxn takes place on the surface of these cells

↓

Complement is activated and cytolysis occurs.

Eg:- thrombocytopenia, aplastic anemia, hemolysis.

Type III :- (Retarded, Arthus) Reactions :-

Mediated by circulating antibodies (IgG)

↓

AG: AB complexes bind complement and precipitate on vascular endothelium giving rise to a destructive inflammatory response.

↓

Manifestations are rashes, serum sickness, Steven-Johnson Syndrome etc.

Cell mediated :-

Type IV (delayed hypersensitivity) Rxns :-

Mediated through production of sensitized T- lymphocytes carrying receptors for AG.

↓

On Contact with the AG, these T cells produce lymphokines which attract granulocytes

↓

generate an inflammatory response

Eg:- Rashes,
Contact dermatitis
Fever.

- This rxn generally takes >12 hours to develop.

Photosensitivity :-

It is a cutaneous reaction resulting from drug induced sensitization of skin to UV radiation.

Types

(1) Phototoxic

(2) Photoallergic

(1) Phototoxic :- Drug or its metabolites accumulates in skin, absorb light and undergoes a photochemical reaction followed by a photobiological reaction resulting in local tissue damage.

ie erythema, edema, blistering followed by hyperpigmentation and desquamation.

- Shorter wave lengths (290-320 nm, UV-B) are responsible.
- Drugs involved are :- Tetracyclins and tar products.
- These are more common than photoallergic reaction.

(2) Photoallergic :- Drug or its metabolite induces a cell mediated immune response which on exposure to light of longer wave length (320-400 nm, UV-A) produces a eczema type reactions.

Drugs involved are :- Sulfonamides, Sulfonylureas, Chloroquine etc.

Drug Dependence :-

Drugs capable of altering mood and feelings are liable to repetitive use to derive euphoria, withdrawal from reality, social adjustment etc.

There are various forms :-

(1) Psychological dependence :- It is said to have developed when the individual believes that optimal state of well being is achieved only through the

The actions of the drug.
It also accompanies all patterns of self medication.

Physical dependence :- It is an altered physiological state produced by repeated administration of a drug which necessitates the continued presence of drug to maintain physiological equilibrium.

Drug Abuse :- Refers to use of a drug by self medication in a manner and amount that deviates from approved medical and social patterns in a given culture at a given time

For regulatory agencies, drug abuse refers to any use of an ilicit drug.

Drug addiction :- It is a pattern of compulsive drug use characterised by overwhelming involvement with the use of the drug.

eg:- Amphetamines, Cannabis are drugs which produce addiction. but little/no physical dependence.

Drug Habituation :- It denotes less intensive involvement with drug, so that its withdrawal produces only mild discomfort. Consumption of tea, coffee, tobacco,

are regarded habituating, physical dependence is absent.

Drug Withdrawal Reactions :-

Physical and mental symptoms that occur after stopping or reducing intake of a drug.

eg :-

(1) Worsening of angina pectoris, precipitation of myocardial infarction may result from stoppage of β- blockers.

(2) Frequency of seizures may increase on sudden withdrawal of an anti-epileptic.

Teratogenicity :-

It refers to capacity of a drug to cause foetal abnormalities when administered to the pregnant mother.

The agent or drug which causes teratogenicity, itself is called as "Teratogen."

Drugs can affect the foetus at 3 stages:-

(1) Fertilization and implanation

(2) Organogenesis

(3) Growth and development.

(1) Fertilization and Implantation - Conception to 17 days - failure of pregnancy which often goes unnoticed.

(2) Organogenesis :- 18 to 55 days of gestation - most vulnerable period, deformities are produced.

(3) Growth and development :- 56 days onwards, - developmental and functional abnormalities can occur.

eg:- ACE inhibitors can cause hypoplasia of organs, specially lungs and kidneys.

Mutagenicity and Carcinogenicity :-

It refers to capacity of a drug to cause genetic defects and cancer respectively.

Usually oxidation of the drug results in the production of reactive intermediates which affect genes and many cause structural changes in the chromosomes.

Drug induced diseases :- These are also called Iatrogenic (physician-induced) diseases and are functional disturbances caused by drugs which persist even after the offending drug has been withdrawn and largely eliminated

eg:- Peptic ulcer by Corticosteroids
Hepatitis by Isoniazid.

Renal Clearance :-

Elimination of drugs by the kidneys is best quantified by the renal clearance (CL_R).

This is defined as, "the volume of plasma containing the amount of substance that is removed from the body by kidneys in unit time.

It is calculated from plasma concentration C_p, the Urinary concentration C_u, and the rate of flow of Urine V_u by the equation;

$$CL_R = \frac{C_u \times V_u}{C_p}$$

CL_R varies greatly for different drugs, and is quantified renal clearance.